Organophosphorus poisoning (acute)

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QUESTIONS

INTERVENTIONS

TREATMENTS

Footnote

*Based on consensus, RCTs would be considered unethical.

Key points

- Acetylcholinesterase inhibition by organophosphorus pesticides or nerve gases can cause acute parasympathetic system dysfunction, muscle weakness, seizures, coma, and respiratory failure.

  Prognosis depends on the dose and relative toxicity of the specific compound, as well as pharmacokinetic factors.

- Initial resuscitation, then atropine and oxygen, are considered to be the mainstays of treatment, although good quality studies to show benefit have not been found.

  We don't know the optimum dose of atropine to give, but common clinical practice is to administer sufficient to keep the heart rate greater than 80 beats per minute, systolic blood pressure above 80mmHg, and the lungs clear.

  Glycopyrronium bromide may be as effective as atropine in preventing death, with fewer adverse effects, although no adequately powered studies have been done.

- Washing the poisoned person and removing contaminated clothes is a sensible approach, but no studies have been done to evaluate benefit.

  Healthcare workers should ensure that washing does not distract them from other treatment priorities, and should protect themselves from contamination.

- Benzodiazepines are considered to be standard treatment to control organophosphorus induced seizures, although no studies have been found.

- We don't know whether activated charcoal, alpha$_2$ adrenergic receptor agonists (clonidine), butyrylcholinesterase replacement therapy using fresh frozen plasma or plasmapheresis, magnesium sulphate, N-methyl-D-aspartate receptor antagonists, organophosphorus hydrolases, sodium bicarbonate, milk and other "home remedies" taken soon after ingestion, cathartics, or extracorporeal clearance improve outcomes.

  Oximes have not been shown to improve outcomes, but studies have been of poor quality so a definite conclusion cannot be made.

  Potential benefits from gastric lavage or ipecacuanha are likely to be outweighed by the risks of harm, such as aspiration.

DEFINITION Acute organophosphorus poisoning occurs after dermal, respiratory, or oral exposure to either low volatility pesticides (e.g. chlorpyrifos, dimethoate) or high volatility nerve gases (e.g. sarin, tabun).

Inhibition of acetylcholinesterase at synapses results in accumulation of acetylcholine and overactivation of acetylcholine receptors at the neuromuscular junction and in the autonomic and central nervous systems. [1] Early clinical features (the acute cholinergic crisis) reflect involvement of the parasympathetic system and include bronchorrhoea, bronchospasm, miosis, salivation, defecation, urination, and hypotension. Features indicating involvement of the neuromuscular junction (muscle weakness and fasciculations) and central nervous system (seizures, coma, and respiratory failure) are common at this stage. Respiratory failure may also occur many hours later, either separated in time from the cholinergic crisis (intermediate syndrome [2]) or merged into the acute cholinergic crisis. [3] The pathophysiology of this late respiratory failure seems to involve downregulation of nicotinic acetylcholine receptors. [2] [3] Intermediate syndrome is particularly important since people who are apparently well can progress rapidly to respiratory arrest. A late motor or motor/sensory peripheral neuropathy can develop after recovery from acute poisoning with some organophosphorus pesticides. [1] Acute poisoning may result in long term neurological and psychiatric effects but the evidence is still unclear. [4] [5] There are differences between pesticides in the clinical syndrome they produce and in the frequency and timing of respiratory failure and death. [3] [6] [7]

INCIDENCE/ PREVALENCE

Most cases occur in the developing world as a result of occupational or deliberate exposure to organophosphorus pesticides. [8] Although data are sparse, organophosphorus pesticides seem to be the most important cause of death from deliberate self poisoning worldwide, causing about 200 000 deaths each year. [9] For example, in Sri Lanka, about 10 000–20 000 admissions to hospital for organophosphorus poisoning occur each year. Of these, at least 10% die. In most cases, the poisoning is intentional. [10] Case mortality across the developing world is commonly greater than 20%. [9] In Central America, occupational poisoning is reported to be more common than intentional poisoning, and deaths are fewer. [11] Deaths from organophosphorus nerve gases occurred during the Iran–Iraq war. [12] Military or terrorist action with these chemical weapons remains possible. Twelve people died in a terrorist attack in Tokyo and probably thousands died in Iran after military use.

AETIOLOGY/ RISK FACTORS

The widespread accessibility of pesticides in rural parts of the developing world makes them easy options for acts of self harm. [9] Occupational exposure is usually because of insufficient or inappropriate protective equipment. [8]

PROGNOSIS

There are no validated scoring systems for categorising severity or predicting outcome of acute organophosphorus poisoning. The highly variable natural history and difficulty in determining the dose and specific organophosphorus compound ingested make predicting outcome for an individual person inaccurate and potentially hazardous, because people admitted in good condition can deteriorate rapidly and require intubation and mechanical ventilation. Prognosis in acute self poisoning is likely to depend on dose and toxicity of the specific organophosphorus compound that has been ingested (e.g. neurotoxicity potential, half life, rate of aging, whether activation to the toxic compound is required (e.g. parathion to paraoxon [pro-poison]), and whether it is dimethylated or diethylated [see comment on oximes, p 9]). [7] [13] Prognosis in occupational exposure is better because the dose is normally smaller and the route is dermal.

AIMS OF INTERVENTION

To prevent mortality; to reduce rates of intubation (with or without ventilation), pneumonia, and delayed polyneuropathy; and to reduce the duration of ventilation and intensive care.

OUTCOMES

Mortality; rates of intubation, pneumonia, intermediate syndrome, delayed polyneuropathy; and duration of ventilation or intensive care.

METHODS

BMJ Clinical Evidence search and appraisal August 2006. The following databases were used to identify studies for this review: Medline 1966 to August 2006, Embase 1980 to August 2006, and The Cochrane Library, Issue 3, 2006 (all databases). Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) – for all databases, Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved were assessed independently by two information specialists using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews, RCTs, and cohort studies in any language, including “open” (non-blinded) RCTs, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow up required to include studies. Relevant observational studies were also sent for use in the background, comments, and harms sections. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. The contributors also searched Medline,

Embase, and Cochrane databases; hand searched toxicological and Indian journals (search date 2005); and contacted experts in the field to identify unpublished studies.

QUESTION What are the effects of treatments for acute organophosphorus poisoning?

OPTION ATROPINE

Mortality
Compared with glycopyrronium bromide We don't know if atropine and glycopyrronium bromide differ in their effectiveness at reducing mortality in people with acute organophosphorus poisoning, as we found insufficient evidence from one small RCT (low quality evidence).

Need for ventilation
Compared with glycopyrronium bromide We don't know if atropine is more effective than glycopyrronium bromide at reducing the proportion of people with acute organophosphorus poisoning who require ventilation, as we found insufficient evidence from one small RCT (low quality evidence).

Pneumonia
Compared with glycopyrronium bromide We don't know if atropine is more effective than glycopyrronium bromide at reducing respiratory infections rates in people with acute organophosphorus poisoning, as we found insufficient evidence from one small RCT (very low-quality evidence).

Note
Although we found no RCTs comparing atropine versus placebo, consensus holds that the effectiveness of atropine is beyond question, so it would be unethical to perform such an RCT. Many case series found that atropine reversed the early muscarinic effects of acute organophosphorus poisoning. Atropine and oxygen are the mainstays of treatment for acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits:

Atropine versus placebo:
We found no systematic review, RCTs, or cohort studies (see comment below). Many case series found that atropine reversed the early muscarinic effects of acute organophosphorus poisoning. [14]

Atropine versus glycopyrronium bromide:
See benefits of glycopyrronium bromide, p 4 .

Harms:

We found no studies of sufficient quality assessing adverse effects in people with acute organophosphorus poisoning receiving atropine. Excessive treatment with atropine results in toxicity, characterised by confusion and tachycardia. [14] In hypoxic people, supplemental oxygen may reduce the risk of atropine induced ventricular tachycardias.

Comment:

Atropine competes with excess acetylcholine at muscarinic acetylcholine receptors.

Clinical guide:
Although we found no RCTs, consensus holds that the effectiveness of atropine is beyond question, so it would be unethical to perform an RCT comparing atropine versus placebo. Atropine and oxygen are the mainstays of treatment for acute organophosphorus poisoning. Sufficient atropine to stabilise the person should be given rapidly.

Dosage and administration:
The optimum dose of atropine has not been determined. [15] It varies among poisoned people because of variation in the dose and organophosphorus compound taken and possibly because of coadministration of an oxime (oximes have been proposed to have anticholinergic action at high dose; see oximes, p 9). [16] The first doses are given as boluses to reverse the muscarinic signs (0.6–3.0 mg iv depending on severity; in the primary care situation, an autoinjector can be used that supplies 2 mg im). Since organophosphorus deaths result from cardiorespiratory failure, recent Sri Lankan studies have aimed to give sufficient atropine rapidly to improve cardiovascular function (systolic blood pressure > 80 mm Hg, pulse > 80 beats a minute) and respiratory function (treat bronchorrhoea and bronchospasm). [15] [16] This atropine dose regimen has not been compared with other regimens with different end points of atropinisation. Once the person is loaded with atropine, current recommendations are then to set up an atropine infusion [16] at a dose that aims to maintain cardiorespiratory function (see above) and prevent toxicity (normal bowel sounds, no agitation or confusion). [15] [17]

OPTION BENZODIAZEPINES

We found no direct information about benzodiazepines in the treatment of people with organophosphorous poisoning.

Note
Although we found no RCTs comparing benzodiazepines versus placebo, it would be considered unethical to perform such an RCT in people with seizures. Many case series have reported that diazepam controls seizures in acute organophosphorus poisoning. Consensus is that benzodiazepines, such as diazepam, lorazepam, and midazolam, should be the preferred treatment for seizures and for agitation.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or cohort studies. Many case series have reported that diazepam controls seizures in acute organophosphorus poisoning. [18] [19]

Harms: We found no studies of sufficient quality assessing adverse effect rates in people with acute organophosphorus poisoning receiving diazepam. Excessive treatment with diazepam may result in respiratory depression requiring intubation and ventilation. However, this is also a direct complication of organophosphorus poisoning, and it is difficult to distinguish between the two. [18]

Comment: Seizures are believed to be initiated by excess acetylcholine in the brain after inhibition of acetylcholinesterase, with subsequent disruption of other neurotransmitter systems such as glutamate and catecholamines. Benzodiazepines work at gamma-aminobutyric acid receptors. Sufficient atropinisation may help to manage organophosphorus induced seizures. Routine use of benzodiazepines before any seizure occurs has support from animal models, but we found no studies in humans. [20]

Clinical guide:
Consensus is that benzodiazepines, such as diazepam, lorazepam, and midazolam, should be the preferred treatment for seizures and for agitation, [21] and they are widely used. It would now be considered unethical to perform an RCT comparing benzodiazepines versus placebo in people with seizures.

OPTION GLYCOPYRRONIUM BROMIDE (GLYCOPYRROLATE)

Mortality
Compared with atropine We don't know if glycopyrronium bromide and atropine differ in their effectiveness at reducing mortality in people with acute organophosphorus poisoning, as we found insufficient evidence from one small RCT (low quality evidence).

Need for ventilation
Compared with atropine We don't know if glycopyrronium bromide is more effective than atropine at reducing the proportion of people with acute organophosphorus poisoning who require ventilation, as we found insufficient evidence from one small RCT (low quality evidence).

Pneumonia
Compared with atropine We don't know if glycopyrronium bromide is more effective than atropine at reducing respiratory infections rates in people with acute organophosphorus poisoning, as we found insufficient evidence from one small RCT (very low-quality evidence).

Note
Although we found no RCTs comparing glycopyrronium bromide (glycopyrrolate) versus placebo, it is unlikely that such an RCT would be considered ethical unless glycopyrronium bromide and placebo were given in addition to atropine. Consensus is that glycopyrronium bromide can be used in place of atropine, and it may reduce the risk of confusion caused by treatment. However, glycopyrronium bromide is not widely used and may be less effective than atropine at controlling central nervous system complications of organophosphorus poisoning. In some regions, glycopyrronium bromide is combined with atropine to limit the central stimulation produced by atropine.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: **Glycopyrronium bromide versus placebo:**
We found no systematic review or RCTs comparing glycopyrronium bromide versus placebo (see comment below)

Glycopyrronium bromide versus atropine:
We found one small RCT (39 people) comparing glycopyrronium bromide versus atropine. [22] It found no significant difference between atropine and glycopyrronium bromide in case fatality (AR: 1/22 [5%] with atropine *v* 2/17 [12%] with glycopyrronium; RR 0.39, 95% CI 0.04 to 3.91), need for ventilation (AR: 8/22 [36%] with atropine *v* 6/17 [35%] with glycopyrronium; RR 1.03, 95% CI 0.44 to 2.41), or respiratory infection rates (AR: 12/22 [55%] with atropine *v* 5/17 [29%] with glycopyrronium; RR 1.86, 95% CI 0.81 to 4.25). The study may have lacked power to detect clinically important differences in mortality, ventilation, or intermediate syndrome.

Harms: We found no studies of sufficient quality assessing adverse effects in people with acute organophosphorus poisoning receiving glycopyrronium bromide. Treatment with glycopyrronium bromide may result in peripheral anticholinergic effects such as tachycardia, dry mouth, and ileus. [23] When these symptoms arise, treatment is defined as excessive.

Comment: It is unlikely that an RCT comparing glycopyrronium bromide versus placebo would be considered ethical unless glycopyrronium bromide and placebo were given in addition to atropine. Glycopyrronium bromide has similar pharmacological effects to atropine in humans, but is more selective for peripheral cholinergic synapses, resulting in less tachycardia and confusion than occur with atropine. [23] Animal studies found that glycopyrronium bromide was less effective than atropine at controlling bradycardia and central nervous system complications of organophosphorus poisoning. We found no large RCT comparing atropine versus glycopyrronium bromide.

Clinical guide:
Consensus is that glycopyrronium bromide can be used in place of atropine, and it may reduce the risk of confusion caused by treatment. However, glycopyrronium bromide is not widely used and may be less effective than atropine at controlling central nervous system complications of organophosphorus poisoning. In some regions, glycopyrronium bromide is combined with atropine to limit the central stimulation produced by atropine.

OPTION WASHING THE POISONED PERSON AND REMOVING CONTAMINATED CLOTHES

We found no direct information on washing the poisoned person and removing contaminated clothes in people with acute organophosphorus poisoning.

Note
Although we found no RCTs comparing washing and removal of contaminated clothes versus placebo, this seems to be an obvious way to reduce further dermal and mucocutaneous exposure and is widely recommended. Such an RCT would therefore be considered unethical. Consensus is that the poisoned person should be washed carefully once initial resuscitation has been performed and they are stable, and after administration of oxygen and atropine as required. Healthcare workers should carefully protect themselves against contamination.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality. No important adverse effects are envisaged, unless washing the poisoned person distracts healthcare workers from other priorities, such as resuscitation and careful observation for deterioration.

Comment:

Clinical guide:
Absorption of organophosphorus compounds through the skin varies, according to the volatility of the organophosphorus, its solvent, and the temperature and hydration of the skin. [24] Absorption of pesticides seems to be low, with studies of malathion, chlorpyrifos, and diazinon suggesting that less than 5% is absorbed and excreted in the urine. [25] [26] [27] However, washing seems to be an obvious way to reduce further dermal and mucocutaneous exposure and is widely recommended. An RCT would therefore be considered unethical. Consensus is that the poisoned person should be washed carefully once initial resuscitation has been performed and they are stable, and after administration of oxygen and atropine as required. Healthcare workers should protect themselves through the use of gloves, aprons, and eye protection, with careful disposal of contaminated equipment and clothes.

OPTION ACTIVATED CHARCOAL (SINGLE OR MULTIPLE DOSE)

We found no direct information about activated charcoal (in either single or multiple dose regimens) in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Single dose regimens:
We found one non-systematic review that found no human studies examining the effects of single dose activated charcoal specifically in people with organophosphorus poisoning. [28] In people with other forms of poisoning, it found no evidence of benefit. [28]

Multiple dose regimens:
We found one non-systematic review that found no human studies examining the effects of multiple dose activated charcoal specifically in people with organophosphorus poisoning. [29] In people with other forms of poisoning, it found no evidence of benefit. [29]

Harms: We found no studies evaluating adverse effects in people with acute organophosphorus poisoning receiving activated charcoal, and no large, high quality RCTs comparing activated charcoal versus placebo in any form that might allow calculation of rates of adverse effects. Adverse effects of activated charcoal may include aspiration, pneumonia, vomiting, diarrhoea, constipation, ileus, and reduced absorption of oral medication. [28] [29] [30] A large retrospective case series (878 people treated with multiple dose activated charcoal) suggests that rates of adverse events with multiple dose regimens (> 2 doses) are likely to be low (significant pulmonary aspiration in 6/878 [0.6%], 95% CI 0.1% to 1.1%). [31]

Comment: Animal studies indicate that activated charcoal can bind to organophosphorus pesticides. [32] A large RCT comparing single or multiple dose activated charcoal versus placebo in acute organophosphorus pesticide poisoning was completed in 2005; the findings should be reported in 2007. [33]

Clinical guide:
In people who have taken a large amount of pesticide and are seen within 1 hour, consensus is that a single dose of activated charcoal may offer benefit after gastric lavage.

OPTION ALPHA2 ADRENERGIC RECEPTOR AGONISTS

We found no direct information about alpha$_2$ adrenergic receptor agonists in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality assessing adverse effects in people with acute organophosphorus poisoning receiving clonidine. Adverse effects of clonidine may include sedation, hypotension, bradycardia, and (with prolonged use) rebound hypertension. [34]

Comment: Clonidine inhibits the release of acetylcholine from cholinergic neurones and has alpha$_2$ adrenergic agonist effects. Animal studies found that pretreatment with clonidine improves survival after organophosphorus poisoning; combination with atropine was more than additive. [35] This treatment has not yet been studied in organophosphorus poisoning in humans.

Clinical guide:
There is currently insufficient evidence to recommend the use of clonidine in people with organophosphorus poisoning.

OPTION BUTYRYLCHOLINESTERASE REPLACEMENT THERAPY New

We found no direct information about butyrylcholinesterase replacement therapy (such as with fresh frozen plasma or plasmapheresis) in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found one systematic review (search date 2002) of the effectiveness of fresh frozen plasma, but it found no RCTs in people with acute organophosphorus poisoning. [36] We found one non-systematic review of the effectiveness of plasmapheresis, but it did not report on its use in people with acute organophosphorus poisoning. [37]

Harms: Neither review found any good quality RCTs reporting adverse effects of butyrylcholinesterase replacement therapy in people with acute organophosphorus poisoning. [36] Serious adverse effects associated with treatment include transfusion associated lung injury [38] and hypotension. [37]

Comment: The rationale behind the use of fresh frozen plasma or plasmapheresis in people with organophosphorus poisoning is that they may reduce high blood pesticide concentrations by increasing plasma levels of the enzyme butyrylcholinesterase (plasmapheresis may also remove some poison if the responsible organophosphorus pesticide has a small volume of distribution, see extracorporeal clearance, p 7). Organophosphorus pesticides bind to and inhibit butyrylcholinesterase in plasma, reducing the amount of pesticide available to inhibit the more clinically important acetylcholinesterase. However, since butyrylcholinesterase is generally sensitive to organophosphorus pesticides, it is usually rapidly used up in moderate to severe poisoning. Replacement of butyrylcholinesterase by administration of fresh frozen plasma or by plasmapheresis should increase the level of enzyme in the blood and neutralise some pesticide. However, whether sufficient butyrylcholinesterase can be given to produce clinical benefit is unknown. A small controlled study (12 people given plasma and 21 people not given plasma) has reported benefit of fresh frozen plasma but it was not an RCT and allocation decisions were unclear. [39] The same researchers reported raised plasma butyrylcholinesterase activity in one poisoned person after plasmapheresis. [40] Since these sources of butyrylcholinesterase are reasonably affordable and available, it is important to determine whether butyrylcholinesterase replacement therapy is effective. One study (in Chinese, with only the abstract available in English) suggested that butyrylcholinesterase activity in fresh frozen plasma falls rapidly and that such plasma should be used within 1 day of donation. [41] Further studies are required to confirm this finding. Use of fresh frozen plasma or plasmapheresis risks transmission of viral and bacterial infectious agents. Careful screening of blood for known pathogens will reduce but not remove this risk.

Clinical guide:
There is currently insufficient evidence to recommend the use of butyrylcholinesterase replacement therapy in people with organophosphorus poisoning.

OPTION EXTRACORPOREAL CLEARANCE New

We found no direct information about extracorporeal clearance in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality to assess adverse effects of extracorporeal clearance in organophosphorus poisoning.

Comment: Effectiveness of extracorporeal clearance will be affected by the volume of distribution of each organophosphorus poison, which is likely to correlate with fat solubility. Extracorporeal clearance may therefore have some effect for non-fat soluble organophosphorus poisons, such as dimethoate and methamidophos, but little effect for very fat soluble organophosphorus poisons such as fenthion. Future clinical trials of extracorporeal clearance will need to take this variability into account. A Cochrane systematic review of extracorporeal clearance in organophosphorus pesticide poisoning is currently underway. [42]

Clinical guide:
There is currently insufficient evidence to recommend the use of extracorporeal clearance in people with organophosphorus poisoning.

OPTION GASTRIC LAVAGE

We found no direct information about gastric lavage in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality assessing the adverse effects of gastric lavage in people with acute organophosphorus poisoning, and no large, high quality RCTs comparing gastric lavage versus placebo in any form of poisoning that might allow calculation of rates of adverse effects. Adverse effects of gastric lavage may include aspiration, hypoxia, laryngeal spasm, and oesophageal

perforation. [43] Adverse effects are common when gastric lavage is performed in physically restrained, non-consenting people without careful control of the airway.

Comment: One non-systematic review identified no studies examining the effects of gastric lavage specifically in people with organophosphorus poisoning. [43] In people with other forms of poisoning, it found no evidence of benefit. [43] A small cohort study of gastric lavage in non-consenting people poisoned with pesticides or plants is currently in press. [44]

Clinical guide:
Gastric lavage may delay administration of activated charcoal and specific treatment for organophosphorus poisoning. It is unclear how long organophosphorus pesticides remain in the stomach after ingestion. If future studies indicate that a substantial proportion of organophosphorus remains in the stomach by the time of admission to hospital, it may be appropriate to conduct an RCT to assess gastric lavage (performed as recommended [43]) after protection of the airway. In people who have taken a large amount of pesticide and are seen within 1–2 hours, consensus is that careful insertion of a nasogastric tube to drain the stomach and perform a brief gastric lavage may offer benefit in people who consent to this treatment or are unconscious and have had their airway protected.

OPTION MAGNESIUM SULPHATE

We found no direct information about magnesium sulphate in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality to assess adverse effects of magnesium sulphate in organophosphorus poisoning. One large, high quality RCT (10 141 women) of magnesium sulphate in eclampsia (4 g loading dose then 1 g/hour for 24 hours) found few serious adverse effects from magnesium sulphate. [45] The most frequent adverse effects are bradycardia and low blood pressure owing to cardiovascular effects, and respiratory depression, weakness, and loss of deep tendon reflexes in the short term owing to impaired neuromuscular transmission. [46]

Comment: Magnesium sulphate is an inhibitor of acetylcholine release in the central nervous system and at peripheral sympathetic and parasympathetic synapses. [47] The administration of magnesium to animals poisoned with organophosphorus pesticides improves outcome, possibly owing to a favourable effect on neuromuscular junction block or increased hydrolysis of some pesticides. [48] The use of magnesium in acute organophosphorus poisoning in humans has been reported in two small studies. [49] [50] In the first study, intravenous administration of magnesium sulphate 4 g to four people produced some improvement in neuromuscular function in two people. [49] The second non-randomised comparative study reported that magnesium decreased mortality compared with usual care (0/11 [0%] with magnesium *v* 5/34 [14.7%] with usual care; $P < 0.01$). [50] However, the study was very small, allocation was not randomised (every fourth eligible person received magnesium sulphate), and the dose of magnesium sulphate used and other aspects of the methodology were incompletely described in the publication. Therefore, these results should be interpreted with caution.

Clinical guide:
There is currently insufficient evidence to recommend the use of magnesium sulphate in people with organophosphorus poisoning.

OPTION MILK OR OTHER HOME REMEDY SOON AFTER ORAL ORGANOPHOSPHORUS EXPOSURE

We found no direct information about giving a "home remedy" soon after the ingestion.

Note
Consensus is that administration of large amounts of fluid soon after the poisoning should be discouraged.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality assessing adverse effects.

Comment:

Clinical guide:
The lay practice of giving a "home remedy" soon after ingestion, before bringing the poisoned person to hospital, is common in many parts of the world. Problems may occur when large volumes of fluid are given "to dilute the poison" or to make the person vomit. Gastric emptying of a fluid is proportional to volume. Therefore, increasing the volume of fluid in the stomach may increase the rate of emptying into the small bowel where the pesticide is absorbed. Giving fluids therefore risks speeding the onset of poisoning and causing respiratory arrest before the person arrives at a healthcare facility. Consensus is that administration of large amounts of fluid soon after the poisoning should be discouraged.

OPTION N-METHYL-D-ASPARTATE RECEPTOR ANTAGONISTS

We found no direct information about N-methyl-D-aspartate receptor antagonists in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of adverse effects in people with acute organophosphorus poisoning receiving N-methyl-D-aspartate (NMDA) receptor antagonists. A dose ranging clinical study found that adverse effects of NMDA receptor antagonists include dizziness, vomiting, nausea, stupor, agitation, and hallucinations. [51]

Comment: Primate studies found that treating organophosphorus nerve gas poisoning with NMDA receptor antagonists, such as gacyclidine, improved clinical recovery, reduced neural death, and improved electroencephalogram activity. [52]

Clinical guide:
There is currently insufficient evidence to recommend the use of NMDA receptor antagonists in people with organophosphorus poisoning.

OPTION ORGANOPHOSPHORUS HYDROLASES

We found no direct information about organophosphorus hydrolases in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality assessing adverse effects.

Comment: Oxime efficacy is normally limited by the presence of high pesticide concentrations, which reinhibit acetylcholinesterases that have been reactivated by the oximes. [53] A method of rapidly reducing pesticide concentrations could potentially allow oximes to be more effective. Animal studies found that organophosphorus hydrolases (such as mammalian paraoxanase or the bacterial hydrolase isolated from *Pseudomonas* species) cleaved organophosphorus compounds, lowering blood and tissue concentrations of organophosphorus. [54] [55] These may prove beneficial for managing people with either pesticide or nerve gas organophosphorus poisoning.

Clinical guide:
Organophosphorus hydrolases have not yet entered clinical development.

OPTION OXIMES

Mortality
Compared with placebo or no oximes or different regimens versus each other We don't know whether oximes are more effective than placebo or no oximes at reducing mortality in people with acute organophosphorus poisoning, or whether bolus or infusion regimens of pralidoxime differ in effectiveness. Evidence was weak, contradictory, and it was difficult to draw reliable conclusions (very low quality evidence).

Need for ventilation
Compared with placebo or no oximes or different regimens versus each other We don't know whether oximes are more effective than placebo or no oximes at reducing the need for ventilation in people with acute organophosphorus

poisoning, or whether bolus or infusion regimens of pralidoxime differ in effectiveness. Evidence was weak, contradictory, and it was difficult to draw reliable conclusions (very low-quality evidence).

Intermediate syndrome

Compared with placebo or no oximes or different regimens versus each other We don't know whether oximes are more effective than placebo or no oximes at reducing inetermediate syndrome in people with acute organophosphorus poisoning, or whether bolus or infusion regimens of pralidoxime differ in effectiveness. Evidence was weak, contradictory, and it was difficult to draw reliable conclusions (very low-quality evidence).

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits:

We found three systematic reviews [56] [57] [58] and one subsequent RCT. [59] The first systematic review (search date 2003) [56] of oximes in people with organophosphorus poisoning, identified two RCTs (182 people) of pralidoxime (reported in 4 publications), which reported different comparisons and outcomes meaning that a meta-analysis could not be performed. [60] [61] [62] [63] Neither of the RCTs found any benefit of pralidoxime (see comments below). The first RCT found that, compared with a bolus of pralidoxime 1 g, an infusion of pralidoxime 12 g (no loading dose, given over 4 days) increased mortality (AR: 8/36 [22%] with pralidoxime 12 g *v* 5/36 [14%] with pralidoxime 1 g; OR 1.77, 95% CI 0.52 to 6.00), intermediate syndrome (20/36 [56%] with pralidoxime 12 g *v* 13/36 [36%] with pralidoxime 1 g; OR not reported), and the need for ventilation (24/36 [67%] with pralidoxime 12 g *v* 17/36 [47%] with pralidoxime 1 g; OR 2.04, 95% CI 0.78 to 5.30); however, confidence intervals were wide, and the difference was not significant. [60] [61] Post hoc analysis of this RCT suggested that people receiving pralidoxime 1 g in the first 12 hours may be less likely to develop intermediate syndrome than those receiving less than 1 g in the first 12 hours (29% with pralidoxime 1 g *v* 51% pralidoxime < 1 g; RR 0.58, 95% CI 0.27 to 1.26). [60] The second RCT (110 people) found that an infusion of pralidoxime 12 g over 3 days increased mortality (AR: 16/55 [29%] with pralidoxime *v* 3/55 [5%] with placebo; RR 5.3, 95% CI 1.7 to 17.3), intermediate syndrome (36/55 [65%] with pralidoxime *v* 19/55 [35%] with placebo; RR 1.9, 95% CI 1.3 to 2.9), and requirement for ventilation compared with placebo (36/55 [67%] with pralidoxime *v* 22/55 [40%] with placebo; RR 1.7, 95% CI 1.1 to 2.4). [62] [63] However, baseline differences in this RCT suggested that more severely poisoned people might have been randomised to the intervention arm. [53] Reporting of methods in both RCTs was poor. In addition, both RCTs [61] [63] included in the review used doses of pralidoxime that were much lower than the regimen currently recommended by the World Health Organization (at least 30 mg/kg loading dose, then 8 mg/kg/hour iv infusion). [16] [64] The second review [57] identified seven clinical studies, three of which were in the first review [56] and the third review [58] identified six clinical studies, two of which were included in the first review [56] and five of which were also included in the second review. [57] Both reviews performed meta-analyses, but included data from retrospective studies with historical controls and non-randomised controlled studies, a methodological weakness that makes interpretation of the results difficult. The first meta-analysis, which separated studies into retrospective and prospective study types, found limited evidence about the effect of oximes on mortality (risk difference [RD] +0.09, 95% CI –0.08 to +0.27), need for ventilation (RD +0.16, 95% CI –0.07 to +0.38), or development of intermediate syndrome (RD +0.16, 95% CI –0.12 to +0.45, absolute data not reported) compared with not receiving oximes. [57] The meta-analysis found heterogeneity between study types but not within individual groups for mortality but no heterogeneity for other outcomes. The second meta-analysis found limited evidence of worse outcomes for people treated with oximes (mortality: 43/162 [26.5%] with oximes *v* 19/167 [11.4%] with no oximes; RR 2.17, 95% CI 1.34 to 3.51; need for ventilation: 67/131 [51.1%] with oximes *v* 45/151 [29.8%] with no oximes; RR 1.53, 95% CI 1.16 to 2.02; intermediate syndrome: 52/110 [47.3%] with oximes *v* 30/92 [32.6%] with no oximes; RR 1.57, 95% CI 1.11 to 2.21). [58] However, the poor quality of all included studies in both meta-analyses suggests that the conclusion that oximes are not effective is unreliable. A further RCT (21 people) of pralidoxime compared with placebo in people with organophosphorus poisoning has recently been published [59] and found no significant difference in mortality (1/10 [10%] with pralidoxime *v* 1/11 [9%] with placebo; P = 0.94), need for ventilation (7/10 [70%] with pralidoxime *v* 4/11 [36%] with placebo; P = 0.12), or complications (4/10 [40%] with pralidoxime *v* 6/11 [55%] with placebo; P = 0.28) with pralidoxime, given at a dose of 4–12 g infused each day over 3 days, compared with placebo.

Harms:

Neither RCT included in the first review reported the incidence of adverse effects in people with acute organophosphorus poisoning receiving oximes. [60] [61] [62] [63] The second [57] and third [58] reviews reported no data on adverse effects occurring in the included studies, and the additional RCT gave no information on harms. [59] Adverse effects of oximes include hypertension, cardiac dysrhythmias (including cardiac arrest after rapid administration), headache, blurred vision, dizziness, and epigastric discomfort. [65] Such adverse effects with pralidoxime have been reported only with either rapid administration or doses greater than 30 mg/kg bolus. It may be difficult to distinguish these adverse effects from the effects of organophosphorus. In one observational clinical study of a different oxime (obidoxime), a high dose regimen (8 mg/kg bolus, then 2 mg/kg/hour infusion)

produced hepatitis in 3/12 (25%) people. [12] Two of six deaths were because of liver failure. The use of pralidoxime (30 mg/kg loading dose, then 8 mg/kg/hour infusion) in eight people in the same study did not produce hepatitis. A more recently developed oxime (HI-6) has also been used in humans, with no reported adverse effects. [66]

Comment:

Oximes (such as pralidoxime, obidoxime, and HI-6) reactivate acetylcholinesterases inhibited by organophosphorus poisoning. [13] [16] Reactivation is limited by aging of the acetylcholinesterases and high concentrations of pesticides. Aging of acetylcholinesterases takes longer with diethyl organophosphorus compounds than with dimethyl organophosphorus compounds. Oximes may therefore be effective if started within about 120 hours for diethyl organophosphorus poisoning and 12 hours for dimethyl organophosphorus poisoning. Treatment may be beneficial if continued for as long as the person is symptomatic because it may take several days for the pesticide concentration to drop below the point at which the rate of reactivation surpasses reinhibition. [13] In vitro and in vivo studies indicate that oximes can reactivate acetylcholinesterase; [13] [67] however, in vitro studies have also revealed mechanisms whereby oximes may be detrimental. [68] Thus far, clinical trials have not yet provided conclusive evidence concerning the clinical benefit or harm from oximes. Since our search date, a further RCT has been published, of a high dose continuous infusion of pralidoxime iodide (1g/hour) compared with an intermittent regime of 1 g over 1 hour every 4 hours, both after initial stabilisation and an initial 2 g loading dose. [69] This RCT found that high dose continuous pralidoxime reduced mortality, the need for ventilation and risk of pneumonia, and will be discussed in detail at our next update. Of note, this is the first RCT to have tested a dose of pralidoxime similar to that recommended by the World Health Organization. [70] A large RCT was started in Sri Lanka in 2004, and the findings are expected to be reported in 2007. [33] One large prospective cohort study examining treatment with pralidoxime for 802 people with chlorpyrifos, dimethoate, or fenthion self poisoning found that acetylcholinesterase inhibited by the two dimethyl organophosphorus pesticides, dimethoate and fenthion, responded poorly to pralidoxime. [7] By contrast, acetylcholinesterase inhibited by the diethyl organophosphorus pesticide, chlorpyrifos, responded well to pralidoxime. [7] Further studies are required to determine whether this variation in response is true for all dimethyl and diethyl organophosphorus pesticides, and for higher doses of oximes. There have been no clinical studies of oximes in people poisoned by nerve gas organophosphorus compounds. These compounds differ in their rates of aging, and compounds such as soman, that age rapidly, probably will not respond to oximes. [71]

Clinical guide:
There is currently mixed evidence regarding the effectiveness of the oximes, and some organophosphorus pesticides do not respond well to oximes. However, until the evidence base for oximes becomes clearer, it is difficult to contradict the World Health Organization guidelines to give high doses of oxime (pralidoxime chloride 30 mg/kg bolus followed by 8–10 mg/kg/hour or obidoxime 250 mg bolus followed by 750 mg/24 hours, both until at least 12 hours after atropine is no longer required) to all people with organophosphorus poisoning. [16] [64]

OPTION SODIUM BICARBONATE

We found no direct information about sodium bicarbonate in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits:

We found one systematic review (search date 2004) of sodium bicarbonate in people with organophosphorus poisoning, which identified no RCTs or observational studies of sufficient quality. [72]

Harms:

The systematic review identified no RCTs or observational studies of sufficient quality assessing adverse effects in people with acute organophosphorus poisoning receiving sodium bicarbonate. [72] Dose dependent adverse effects of sodium bicarbonate may include sodium and fluid overload and decreased oxygen delivery. [73]

Comment:

Studies in animals found that increasing the blood pH with sodium bicarbonate (given orally or iv) reduced mortality from organophosphorus poisoning. [74] [75] This effect is independent of correction of acidosis because it is seen in animals that are not acidotic. Uncontrolled studies conducted in Brazil [75] and Iran [76] have claimed good results with sodium bicarbonate. Its mechanism of action in organophosphorus poisoning is unknown. However, it is unclear whether the limited increase in pH that is possible in vivo is sufficient to make a significant difference.

Clinical guide:
Currently, there is insufficient evidence to recommend the use of sodium bicarbonate in people with organophosphorus poisoning.

OPTION CATHARTICS

We found no direct information about cathartics in people with acute organophosphorus poisoning.

Note
Organophosphorus poisoning itself causes diarrhoea, which can lead to electrolyte imbalance. This may be exacerbated by cathartics, suggesting that the risk of harm may outweigh its potential benefits.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality. Recognised complications of cathartics include electrolyte imbalance and dehydration. [77]

Comment: One non-systematic review identified no studies examining the effects of cathartics specifically in people with organophosphorus poisoning. [77] The review found no studies assessing clinical outcomes after cathartics in people with any other type of poisoning. [77]

Clinical guide:
Cathartics have been used to treat organophosphorus poisoning because they are believed to speed the passage of poisons in general out of the gastrointestinal tract. [77] Reduced transit time reduces the absorption of poison. However, organophosphorus poisoning itself causes diarrhoea, which can lead to electrolyte imbalance. This may be exacerbated by cathartics, suggesting that the risk of harm may outweigh its potential benefits. There is no reason to believe that cathartics will benefit people poisoned with organophosphorus pesticide.

OPTION IPECACUANHA (IPECAC)

We found no direct information about ipecacuanha (ipecac) in people with acute organophosphorus poisoning.

Note
Administration of ipecacuanha may delay administration of activated charcoal and specific treatment for organophosphorus poisoning, in addition to increasing the risk of aspiration. Consensus is that ipecacuanha should not be given to people poisoned with organophosphorus pesticides.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 16 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality assessing the adverse effects of ipecacuanha in people with acute organophosphorus poisoning, and no large, high quality RCTs comparing ipecacuanha versus placebo in any form of poisoning that might have allowed calculation of rates of adverse effects. Adverse effects of ipecacuanha may include aspiration, diarrhoea, ileus, dysrhythmias during vomiting, dystonia from treatment of vomiting, and haematemesis from vomiting. [78] Use of ipecacuanha in acute organophosphorus poisoning may be particularly hazardous because most organophosphorus compounds are dissolved in aromatic hydrocarbons, which cause serious harm if aspirated (see comment below). [78]

Comment: One non-systematic review, which included experimental and observational studies, identified no studies examining the effects of ipecacuanha specifically in people with organophosphorus poisoning. In people with other forms of poisoning, it found no evidence of benefit. [78]

Clinical guide:
Administration of ipecacuanha may delay administration of activated charcoal and specific treatment for organophosphorus poisoning, in addition to increasing the risk of aspiration. Consensus is that ipecacuanha should not be given to people poisoned with organophosphorus pesticides.

GLOSSARY

Acetylcholinesterase An enzyme that cleaves acetylcholine.
Aging Esterases (such as acetylcholinesterase and neuropathy target esterase) are inhibited by organophosphorus compounds through phosphorylation. Inhibited acetylcholinesterase reactivates spontaneously at very slow rates; oximes speed up this reaction. However, phosphorylated acetylcholinesterase may lose an alkyl side chain non-enzymatically, leaving a hydroxyl group in its place (“aging”). Regeneration is then no longer possible. The half-life of aging is as fast as 8 minutes with the nerve gas soman but as slow as 33 hours for diethyl pesticides such as chlorpyrifos.

Atropinisation Giving atropine until it reaches a sufficiently high blood concentration to suppress cholinergic signs clinically.
Pro-poisons Some organophosphorus pesticides require activation in vivo to become toxic.
Rates of aging The rate depends on the identity of the alkyl side chains on each organophosphorus. Those with two methyl groups will age faster than those with two ethyl groups and thus become unresponsive to oximes at an earlier time point.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

New option added Butyrylcholinesterase replacement therapy.
New option added Extracorporeal clearance.
Oximes One systematic review added that found no benefit from oximes compared with no oximes in reducing mortality, the need for ventilation, or development of intermediate syndrome from studies of poor methodological quality. [57] One systematic review added that found an increased risk of mortality, need for ventilation, and development of intermediate syndrome with oximes compared with no oximes, from studies of poor methodological quality. [58] One small RCT added that found no reduced risk of death, need for ventilation, or complications with pralidoxime compared with placebo. [59] Categorisation unchanged (unknown effectiveness).
Cathartics Recategorised from Likely to be ineffective or harmful to Unlikely to be beneficial (based on consensus).

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TABLE **GRADE evaluation of interventions for organophosphorus poisoning**

Important outcomes	**Mortality, pneumonia, intermediate syndrome, need for ventilation, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for acute organophosphorus poisoning?									
1 (39) [22]	Mortality	Glycopyrronium bromide v atropine	4	-1	0	-1	0	Low	Quality points deducted for sparse data. Directness point deducted for small number of events
1 (39) [22]	Need for ventilation	Glycopyrronium bromide v atropine	4	-1	0	-1	0	Low	Quality points deducted for sparse data. Directness point deducted for small number of events
1 (39) [22]	Pneumonia	Glycopyrronium bromide v atropine	4	-1	0	-2	0	Very low	Quality points deducted for sparse data. Directness points deducted for small number of events and for proxy outcome (respiratory infection rates)
At least 8 (at least 203) [57] [58] [60] [61] [62] [63] [59]	Mortality	Oximes v placebo or no oximes or different regimens v each other	4	-3	-1	-1	0	Very low	Quality points deducted for inclusion of observational data, incomplete reporting of results, and weak methods of included RCTs. Consistency point deducted for conflicting results. Directness point deducted for lower than recommended dose used in some studies affecting generalisability of results
At least 7 (at least 182) [57] [58] [60] [61] [62] [63]	Intermediate syndrome	Oximes v placebo or no oximes or different regimens v each other	4	-3	-1	-1	0	Very low	Quality points deducted for inclusion of observational data, incomplete reporting of results, and weak methods of included RCTs. Consistency point deducted for conflicting results. Directness point deducted for lower than recommended dose used in some studies affecting generalisability of results
At least 8 (at least 203) [57] [58] [60] [61] [62] [63] [59]	Need for ventilation	Oximes v placebo or no oximes or different regimens v each other	4	-3	-1	-1	0	Very low	Quality points deducted for inclusion of observational data, incomplete reporting of results, and weak methods of included RCTs. Consistency point deducted for conflicting results. Directness point deducted for lower than recommended dose used in some studies affecting generalisability of results

Type of evidence: 4 = RCT; 2 = Observational Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio